Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Edoxaban improves acute venous thromboembolism while preserving protein C and protein S levels

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ARTICLE INFO

Article history:
Received 18 April 2017
Received in revised form 23 August 2017
Accepted 6 September 2017
Available online xxx

Keywords:
Acute venous thromboembolism
Anticoagulants
Factor Xa inhibitor

ABSTRACT

Background: It is well known that warfarin inhibits the synthesis of vitamin K-dependent anticoagulants, including thrombin, protein C and S, and factor Xa, leading, paradoxically, to an initial hypercoagulable state. Edoxaban, a direct inhibitor of activated factor X is widely used for the treatment of acute venous thromboembolism (VTE). However, the effect of edoxaban on circulating coagulation factors, in patients with acute VTE, remains unknown.

Methods and results: We enrolled 57 patients with acute VTE with/without pulmonary embolism treated with edoxaban ($n = 37$) or warfarin ($n = 20$) in a clinical setting. Before treatment and 2 weeks after treatment, we evaluated thrombotic burden using ultrasound or computed tomography angiography. We also evaluated thrombin generation, represented by prothrombin fragment F1 + 2; thrombus degradation, represented by D-dimer; and levels of anticoagulants, including protein C, protein S, and antithrombin III. Both edoxaban and warfarin treatment improved thrombotic burden and decreased prothrombin fragment F1 + 2, and D-dimer. Edoxaban treatment preserved protein C and protein S levels. In contrast, warfarin decreased protein C and protein S levels. Neither treatment affected antithrombin III.

Conclusions: Edoxaban improves VTE while preserving protein C and protein S levels, thereby indicating that edoxaban improves thrombotic burden while maintaining levels of anticoagulants.

Introduction

Acute venous thromboembolism (VTE) including deep vein thrombosis (DVT) and acute pulmonary embolism (PE) contributes to significant morbidity and mortality, especially in hospitalized patients with underlying disease. The standard treatment of VTE consists of unfractionated heparin/low-molecular-weight heparin followed by warfarin, a vitamin K antagonist [1,2]. However, warfarin paradoxically worsens the coagulation status during the initial phase through inhibiting protein C (PC) and protein S (PS), since the latter are vitamin K-dependent anticoagulants with a shorter half-life than other anticoagulants [3].

PC is activated by thrombin-thrombomodulin, together with PS, which acts as a co-enzyme of PC, and leads to degradation of factor V and VIII, thereby limiting thrombin formation through a negative feedback mechanism. In the acute phase of VTE, large amounts of

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https://doi.org/10.1016/j.jjcc.2017.09.009
0914-5087/

thrombin are produced through activation of the coagulation cascade, and this reaction is referred to as the thrombin-burst, which results in consumption of PC and PS. Any further decrease in PC and PS levels in acute VTE could be critical [4,5]. Therefore, a new treatment strategy that does not inhibit PC and PS would be of great clinical value.

Edoxaban, a direct oral inhibitor of activated factor X, is available for the treatment of acute VTE [6]. The Hokusai-VTE study showed that edoxaban was non-inferior to standard therapy with warfarin after initial heparin, with significantly less bleeding [7]. Therefore, previous literature suggests that edoxaban is a novel therapeutic option for the treatment of acute VTE that acts without inhibiting PC and PS, and therefore has the potential to simplify the long-term treatment of patients with VTE [8].

However, it is unknown whether edoxaban affects levels of PC and PS in patients with acute VTE. We hypothesized that edoxaban improves VTE without decreasing the activity of PC and PS, and therefore acts through a different mechanism than warfarin.

Methods

We enrolled 57 consecutive Japanese patients (≥20 years) with acute VTE in the Department of Cardiovascular Medicine at Tokushima University Hospital and in the Department of Internal Medicine or Department of Orthopedics at Shikoku Central Hospital between April 2013 and May 2017.

Patients were treated with edoxaban or warfarin following unfractionated heparin according to the clinical setting and physicians' decision. Edoxaban was administered orally at a dose of 60 mg, once daily, or at a dose of 30 mg, once daily in patients with a creatinine clearance of 30–50 ml per minute, or those with a body weight of 60 kg or less, or in patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors. Warfarin was administered with adjustment of the dose to maintain the international normalized ratio (INR) between 2.0 and 3.0. In high-risk patients for bleeding, target INR was between 1.5 and 2.5 according to the Japanese guideline [9].

Acute VTE was defined as acute, symptomatic DVT involving the popliteal, femoral, or iliac veins, or acute, symptomatic PE (with or without DVT). Thrombus was evaluated by contrast computed tomography (CT) or vascular echography before and 2 weeks after treatment.

The coagulation or anti-coagulation related factors including plasma levels of PC activity and antigen, free PS antigen, antithrombin III (AT III), prothrombin time-international normalized ratio (PT-INR), prothrombin fragment F1 + 2, and D-dimer levels were measured before the treatment and 2 weeks after the treatment.

Plasma levels of PC activity, PC antigen, and free PS antigen were measured at a commercial laboratory (LSI Medience Co.) using a synthetic substrate assay with the HemosIL, a latex photometric immunoassay with LPIA-ACE II, and alatex agglutination turbidimetry with the HaemosIL Free PS, respectively. AT III was measured using a synthetic substrate assay with the CHROMRATE AT III kit (LSI Medience Co., Tokyo, Japan). PT-INR was measured by using a HemosIL RecombiPlasTin 2G reagent (Instrumentation Laboratories, Lexington, MA, USA). The prothrombin fragment F1 + 2 level was measured using enzyme immunoassay at a commercial laboratory (BML Co., Tokyo, Japan) with the Enzygnost F1 + 2 + 2 (monoclonal) kit. D-dimer was measured by using a latex agglutination assay with the LPIA-ACE D-D dimer II kit (LSI Medience Co.).

The exclusion criteria were contraindications to heparin, warfarin, or edoxaban (i.e. active bleeding). In addition, we excluded patients with kidney dysfunction (creatinine clearance < 15 mL/min) and liver dysfunction (aspartate aminotransferase levels of >100 IU/L, alanine aminotransferase levels of >100 IU/L).

This study protocol was approved by the Tokushima University Hospital Ethics Committee and Shikoku Central Hospital Ethics Committee.

Statistical analyses

All data are expressed as means ± standard deviation (SD). Associations between clinical parameters in edoxaban group and warfarin group were determined by the Student's *t*-test or Chi-square tests. Paired *t*-test was used to compare patient's variables at baseline and after edoxaban or warfarin treatment. All statistical analyses were performed using JMP software (version 10; SAS, Cary, NC, USA) and statistical significance was defined as a *p*-value of <0.05.

Results

Clinical characteristics of subjects

The characteristics of all patients are shown in Table 1. The mean dose of edoxaban or warfarin was 35 ± 12 mg, and 2.7 ± 1.2 mg, respectively. The major cause of VTE was orthopedic-related disease (i.e. femoral neck fracture) in edoxaban group and malignant disease in warfarin group. Patients on edoxaban were older than those on warfarin ($p < 0.05$).

Table 1
Clinical characteristics of subjects.

Variables	Edoxaban group	Warfarin group	*p*-Value
Number of patients	37	20	
Age (years)	75 ± 12	67 ± 12	0.01
Male	12 (32%)	6 (30%)	0.85
Body weight (kg)	57 ± 12	57 ± 17	0.67
Body mass index (kg/m^2)	25 ± 5	24 ± 6	0.67
Hemoglobin (g/dL)	10.9 ± 1.8	10.6 ± 2.0	0.54
Serum creatinine (mg/dL)	0.67 ± 0.25	0.73 ± 0.31	0.43
Creatinine clearance (mL/min)	79 ± 40	80 ± 38	0.96
Period of UFH treatment (days)	1.9 ± 3.2	3.1 ± 2.7	0.22
Complication of pulmonary embolism	14 (38%)	11 (55%)	0.21
Cause of VTE			
Orthopedic disease	18 (49%)	5 (25%)	0.08
Malignant disease	10 (27%)	10 (50%)	0.08
Immobility due to benign medical illness	7 (19%)	5 (25%)	0.59
Unprovoked	2 (5%)	0 (0%)	0.29

UFH, unfractionated heparin; VTE, venous thromboembolism.

Please cite this article in press as: Yamazaki H, et al. Edoxaban improves acute venous thromboembolism while preserving protein C and protein S levels. J Cardiol (2017), https://doi.org/10.1016/j.jjcc.2017.09.009